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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,700	CUTTITTA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *19,20 and 44-46* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *19-20, 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims withdrawn from consideration are all embodiments other than Method with SEQ ID NOs 2 or 3.

1. The compliant response filed August 19, 2003 (Paper No. 13) in response to the Office Action of July 17, 2003 (Paper No. 12) and the Response, filed July 9, 2003 (Paper No. 11) to the Restriction Requirement mailed May 7, 2003 (Paper No. 10) are acknowledged and have been entered. Claims 19-20, 44-46 drawn to a method of treating/preventing breast cancer with an ntibody to at least one of SEQ ID NOS 2 or 3 are currently under examination

2. Applicant's election with traverse of Group C2, claims 19-20, a method of using an antibody to treat or prevent breast cancer is acknowledged. Applicant points out that the election of this single species only applies if no generic claim is finally held to be allowable. It is noted that Group C2 is not a species, but rather a distinct invention which is linked to other inventions through newly added linking claim 44. Should Claim 44 be found allowable as originally filed, the restriction requirement as to the linked inventions will be withdrawn. Further, in view of Applicant's arguments, the inventions drawn to SEQ ID NOS 2 and 3 are hereby rejoined. Claims 19-20 and 44-46 will be examined as they are drawn to a method of treating/preventing breast cancer with an antibody to at least one of SEQ ID NOS 2 or 3

Specification

3. The specification on page 1 should be amended to claim benefit of the parent applications. Further, the status of each parent application, i.e. "now abandoned" or "now US Patent No" must be delineated

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

5. Claims 19, 20, 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as claimed.

The claims are drawn to a method of inhibiting or suppressing growth of a tumor cell/breast tumor cell in a patient which reads on both prevention and treatment of breast cancer.

The specification teaches that it is an object of the present invention to provide methods for the prevention and treatment of breast cancer by contacting cancerous cells with an effective amount of anti-AM antibodies (p. 4, lines 22-30). The MCF7 breast cancer cell line, was shown to express AM message (p. 16, lines 10-15) as did the normal tissue tested (page 16, lines 30-35). It is noted that neither normal breast tissue nor primary breast cancer were assayed. Mab-G6, antibody raised to SEQ ID NO:3, was shown to inhibit growth of MCF-7 cells at the highest concentration of MAb-G6, that is 100 ug/ml (p. 19, lines 16-30). The specification states that synthetic AM binding to MCF7 was not competitively blocked by PO72 (SEQ ID NO:3) but was competitively inhibited by AM (p. 20, lines 5-20). (It is

noted that although the specification points to figures 28C and D it appears that the specification was filed without Figures 28C and D. A review of the published patent also revealed that the patent was printed without figures 28C and D. It must therefore be assumed that figures 28C and D were not submitted with the applications as originally filed.). MCF7 cells express high affinity receptors for AM and respond to exogenous AM by increasing intracellular cAMP (p. 40, lines 14-26). The specification exemplifies cell culture studies wherein 100 micrograms/ml of Mab-G6 inhibited MCF-7 growth *in vitro* (p. 57), said inhibition was substantially reduced when cells were incubated with 10 micrograms/ml of Mab-G6 plus AM (p. 57, see Table 5). Exogenous addition of AM to MCF7 cell line was ineffective in stimulating growth of cells. Since the test cell lines were known to produce authentic AM peptide, it was assumed that this inability to stimulate growth with extrinsic ligand meant that it had already achieved maximal proliferative effects using its own AM-producing mechanism (p. 60, lines 5-22). . Dose dependent suppression of growth of MCF-7 cell line was observed with addition of Mab-G-6 (p. 61).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide guidance which teaches the feasibility of *in vivo* use for an antibody to SEQ ID NO:2 or 3 for the treatment of breast cancer. All of the exemplification in the specification is drawn specifically to cell culture studies. The enablement of the claimed method appears to be based based solely on *in vitro* data. The art does not recognize a reliable correlation between *in vitro* assay data and effective *in vivo* efficacy for human tumor

immunotherapy using antibodies. This is evidenced Kimmel et al.(J. Neurosurg, 66:161-171, 1987) who teach that *in vitro* assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and cannot duplicate the complex conditions of *in vivo* therapy. Hird et al. teach (in "Genes and Cancer" Carney et al., Ed, John Wiley and Sons Ltd, 1990, pps 83-89) on page 185 that unconjugated antibodies have not yielded satisfactory therapeutic results. The authors further state that *in vitro* studies are useful but cannot be directly translated to apply to the human situation, which is clearly contemplated in the specification, due to differences in metabolic rate, circulation time, tumor bulk, vascularity and other factors which exist. In particular, it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a normal tissue. The *in vitro* experimental data presented is clearly not drawn to subjects with tumor cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer

(Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant *cells in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based only on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, the invention would function as claimed. Further, the artifactural nature of cell culture systems is well known in the art. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized

cells originated from a specific cancer cell (see attached abstract). In addition, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teach that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). It is clear that the unpredictability of using cancer cell lines is well known in the art since Slamon et al, (Cancer Cells, 1989, 7:371-384) specifically teach that for their studies they use clones from actual human tumor tissue because DNA in cell lines can acquire genetic changes *in vitro* that may not be representative of the gene *in vivo*, p. 373, col 1). Thus, based only on the cell culture data presented in the specification, in the absence of data provided from primary tumors and normal controls, no one of skill in the art would believe it more likely than not that AM is in any way associated with the etiology or carcinogenesis of breast cancer or that an antibody to AM could be used for the treatment or prevention of breast cancer. Further, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to

find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of antibody to AM for the treatment or prevention of breast cancer would function as claimed based only on the cell culture data presented. Further, Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents (i.e. antibodies) and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the claimed method would function as claimed based only on the cell culture data disclosed. In addition, Hartwell et al (Science, 1997, 278:64-1068) teach that an effective chemotherapeutic (i.e. antibody) must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular

alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug (antibody) acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065). Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents (i.e. antibodies) that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3) and further specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

The specification clearly teaches that antibody to SEQ ID NO:3 binds not only to MCF7 cells but also to brain, heart, lung and adrenal gland normal tissues. There is no teaching that AM is differentially expressed in normal breast and breast tumor tissues. There is no teaching that antibody to SEQ ID NO:3 is selective for dividing cells. It would appear from the information in the specification that the claimed method is not selective for tumor cells nor would it be expected that the claimed antibody would act only on dividing cells since the specification clearly teaches what appears to be a ubiquitous expression of AM. In particular, Parmiani (Immunology Today, 1993, 14:536-538) teaches that a method whereby both normal and neoplastic cells are destroyed leads to clinically opposite effects, that is autoimmune disease as well as tumor rejection. Parmiani teaches that if an antigen is found that appears to be selectively expressed by a tumor, attempts at therapies drawn specifically to that antigen (in this case AM) should be preceded by careful

tests on the toxic side effects of a possible destruction of normal cells throughout the body (p. 538, col 1).

Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. In addition, it was well known in the art, at the time the invention was made, that *in vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the antibody is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition, anti-tumor agents/antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. This is of particular importance in antibody-related therapies because WO 93/17715

specifically teaches that (1) solid tumors are generally impermeable to antibody-sized molecules; (2) that antibodies that enter the tumor mass do not distribute evenly because of the dense packing of tumor cells; and (3) antigen-deficient mutants can escape being killed by the immunotoxin and regrow (p. 4, lines 10-37), thus the ability to use an effective amount of the claimed antibody to treat breast cancer is unpredictable. Further, as drawn to antibody based anti-tumor therapy, Schlom (in Molecular Foundations of Oncology, 1991, S. Broder, Ed., Williams & Williams, Baltimore, pages 95-134) teaches that for antibody based cancer therapy, the target cells must be considered, that is the number of antigen molecules per cell surface and the number of cells expressing the reactive antigen in the tissue as well as the presence and reactivity of circulating antigen in the blood (p. 98, Table 6.2). The specification clearly teaches the presence of high levels of AM in human plasma (p. 2). Since AM is secreted, even if AM is somehow associated with breast cancer etiology or carcinogenesis and antibody to AM can be used to prevent binding of AM to cancer cells, wherein said binding might in some way be associated with cell proliferation or cancer progression, the serum AM would be expected to sequestered the antibodies and it could not be predicted that sufficient antibody concentrations would reach the target tissue in order to effectively treat breast cancer. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed method will function as claimed with a reasonable expectation of success.

Further, the claims are drawn to preventing breast cancer. This would require administration of the claimed antibody prior to the development of the tumors. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients at risk for developing those tumors. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention will function as claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Claims 19-20, 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and SEQ ID NO:3 and therefore the written description is not commensurate in scope with the claims drawn to methods of using those peptides for the treatment or prevention of breast cancer.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page

1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Although drawn to the DNA arts, the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant rejection. The Courts found that adequate written description requires more than a mere statement that a nucleic acid is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. The specification makes it clear, as disclosed above, that no methods of treatment or prevention were in the hands of the inventors at the time the invention was made. The language of the specification is replete with phrases such as "it is suggested", AM may play a role" AM may be involved", "AM has been implicated". Applicant has clearly not conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. Further, the specification has not presented evidence of actual reduction to practice of any of the claimed treatments or preventions. It is clear from the discussion set forth above that *in vivo* treatments and preventions are highly unpredictable because of the complex nature of the system and it is clear that the nature of the technology is not mature.. *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) have clearly found that the less mature the technology, the more evidence is required to show possession.

Again, as drawn to the DNA arts, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic

statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The finding is clearly relevant to the instant rejection since Applicant appears to be wishing or planning for obtaining the claimed invention. This is insufficient to support the generic claims as provided by the written description guidelines

Therefore only the isolated peptides consisting of SEQ ID Nos: 2 and 3, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 28, 2003